Acromegaly With 'Normal' Growth Hormone Levels

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ACROMEGALY is a syndrome of growth hormone excess that leads to a variety of trophic changes in the tissues of the body. Frequent clinical manifestations of acromegaly include enlargement of the hands, feet, nose and mandible, coarsening of the facial features, excessive perspiration, joint pains and paresthesias.[1] Patients with acromegaly almost always have elevations in serum growth hormone concentrations, but in an occasional patient, serum growth hormone levels are within the normal range. Additionally, radiologic examination shows enlargement of the sella turcica in most of these patients.[1]

We describe the cases of three patients with the typical clinical manifestations of acromegaly whose serum growth hormone levels were not elevated. In addition, in two of these three patients, the pituitary gland was not enlarged on radiographic examination.

Reports of Cases

CASE 1. A 49-year-old man was admitted for the treatment of schizophrenia and alcohol dependence. He had typical acromegalic facial features and on close questioning recalled increasing jaw, hat and shoe size over the prior decade. He also described typical symptoms of a bilateral carpal tunnel syndrome that had been confirmed by electromyography (EMG) at another hospital. On physical examination he had frontal bossing and prognathism. The hands and feet were moist and large with increased amounts of soft tissue. The rest of the examination showed no abnormalities. A fasting plasma glucose level was 200 mg per dl with other routine laboratory tests within normal limits. A fasting serum growth hormone level was 4 ng per ml (normal, < 10). A thyrotropin-releasing hormone (TRH) stimulation test showed a basal growth hormone level of 8.6 ng per ml, increasing to a peak of 29 ng per ml at 45 minutes. A glucose suppression test showed a serum growth hormone level of 7.9 ng per ml 60 minutes after glucose ingestion. Thyroid, adrenal, gonadal and prolactin testing was normal. Skull x-ray films showed an enlarged jaw and large frontal sinuses but the sella turcica was not enlarged. Sella turcica tomograms showed a normal sella with an anteroposterior diameter of 1.5 cm and a depth of 0.8 cm. A computed tomographic (CT) scan showed an area of low density on the right side of the pituitary, consistent with a pituitary adenoma, with no evidence of sella turcica destruction or suprasellar extension. Transsphenoidal exploration of the pituitary gland showed a 2-mm pituitary tumor, which was removed in its entirety. Postoperatively, serum growth hormone values were all less than 3 ng per ml, there was no stimulation of growth hormone secretion after administration of TRH and the symptoms of a bilateral carpal tunnel syndrome disappeared.

ABBREVIATIONS USED IN TEXT
CT = computed tomography
EMG = electromyography
TRH = thyrotropin-releasing hormone

CASE 2. A 41-year-old man, a dermatologist, sought medical attention because of the development of bilateral carpal tunnel syndrome, which was confirmed by EMG. Over the past several years he had noted coarsening of his facial features but said he had not had changes in ring or shoe size, hyperhidrosis or other symptoms associated with acromegaly. On physical examination a prominent brow and coarsening of the facial features were seen in comparison to pictures taken five years previously. His hands were enlarged with increased amounts of soft tissue and he had numbness of his thumb and first two fingers of both hands. There were no other abnormalities noted. Routine laboratory testing was within normal limits except for a fasting glucose level of 158 mg per dl. A fasting serum growth hormone level was 8 ng per ml. A glucose suppression test showed a pronounced abnormality in glucose metabolism with a 120-minute glucose concentration of 336 mg per dl. Serum growth hormone concentrations did not suppress in response to glucose ingestion (60 minutes, 9 ng per ml). Serum growth hormone levels did not increase in response to administration of TRH (0 minutes, 8, 15 minutes, 9, 30 minutes, 8, and 60 minutes, 10 ng per ml). Somatomedin levels were elevated at 5.7 units per ml (0.5 to 2.0 units per ml is the normal range). Thyroid, adrenal, gonadal and prolactin testing was normal. Lateral skull x-ray films did not show an enlarged sella turcica. On CT scan of the pituitary gland there was a radiolucent area measuring 6 mm in diameter, consistent with a pituitary adenoma. The patient's sella turcica was explored via the transsphenoidal approach and a pituitary microadenoma was removed uneventfully. Postoperatively, several serum growth hormone levels were less than 5 ng per ml, and his bilateral carpal tunnel syndromes rapidly resolved.

CASE 3.* The patient, a 56-year-old man, was admitted with a chief complaint of enlargement of his hands and feet that began about 14 years before admission. In addition, he noted increased perspiration with offensive body odor, progressive numbness and weakness in both hands, enlargement of his tongue and mild coarsening of his facial features. On physical examination he had a slightly elevated blood pressure of 150/90 mm of mercury, minimal coarsening of his facial features, an enlarged tongue that filled most of his oropharynx, enlarged hands and feet with increased soft tissue hypertrophy and numbness in the thumb and first two fingers of both hands. Routine laboratory tests were normal. Numerous growth hormone levels were measured that were all less than 10 ng per ml. The serum growth hormone response to insulin hypoglycemia and glucose suppression was normal but the response to both levodopa and TRH administration was abnormal (TRH at 0 minute, 4.2, and 15 minutes, 17.5 ng per ml; levodopa at 0 minute, 7.7, and 60 minutes, 2.1 ng per ml). The somatomedin levels were raised at 2.5 units per

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ml. Lateral skull x-ray films showed an enlarged sella turcica with bulging of the anterior and inferior portions. A pneumoencephalogram showed no evidence of suprasellar extension. The sella turcica was explored via the transsphenoidal approach and an enlarged but grossly normal pituitary gland was exposed. No adenomas were located during careful exploration. Histologic examination of pituitary biopsy specimens failed to show either adenomatous changes or an increase in granulated acidophils. Postoperatively, there was a subjective resolution of symptoms but results of physical examination and repeat laboratory testing of growth hormone dynamics and somatomedin levels were unchanged.

Methods

Growth hormone levels were measured by radioimmunoassay by either Smith Kline & French Laboratories or Consolidated Biomedical Laboratories, a subsidiary of Rohm and Haas Company. The normal growth hormone range in men is 0 to 10 ng per ml. Somatomedins were measured by E. Martin Spencer, MD, by an assay that used human placental membrane as the receptor and radiolabeled somatomedin A purified from human plasma as the ligand. This assay detects somatomedin A and C and the normal level for men is 0.5 to 2.0 units per ml.[2]

Glucose suppression testing was carried out by having the patients fast overnight and then ingest one bottle of glucola (75 grams of glucose). Specimens for growth hormone determinations were obtained at 0 and 60 minutes. Levodopa stimulation consisted of the oral administration of 500 mg of levodopa after an overnight fast. Serum specimens were taken for growth hormone determination at 0, 60 and 90 minutes. The TRH testing consisted of the intravenous administration of 200 μg of TRH with blood specimens for growth hormone determinations taken at 15-minute intervals for one hour.

Discussion

The three patients described in this report all presented with the typical clinical manifestations of acromegaly but in all three cases the serum growth hormone values were within the "normal" range. Over the past decade at our institution, which is *not* a major referral hospital for pituitary tumors, we have diagnosed acromegaly in nine patients. Thus, a third of the patients with acromegaly diagnosed at this hospital in the past decade have had growth hormone levels within the "normal" range. This frequency of acromegaly with "normal" growth hormone levels is considerably higher than that reported in the literature. The incidence of acromegalic patients with "normal" growth hormone concentrations varies from study to study (Table 1), with an average incidence of 4.9% if one combines these series.[3-21]

There are several possible explanations for the high incidence of acromegalic patients with "normal" growth hormone concentrations seen at our institution. First, our hospital is not a major referral center for the treatment of acromegaly or pituitary tumors and, therefore, this incidence of "normal" growth hormone acromegaly is not biased by the referral of only patients with clearly documented disease. It is likely that patients with "normal" hormone values and possible acromegaly are not referred to major centers for definitive diagnosis and treatment. This selection bias would result in an artifactually reduced incidence of acromegaly with "normal" growth hormone levels reported by these major centers.

TABLE 1.—*Number of Untreated Cases of Acromegaly With Growth Hormone Levels < 10 mg/dl Divided by Total Number of Untreated Cases*

Source		*Percent*
Lawrence et al, 1971[3]	0/12	0
Mims and Bethune, 1974[4]	5/62	8
Levin et al, 1974[5]	7/50	14
Williams et al, 1975[6]	4/68	6
Becker et al, 1974[7]	1/12	8
Pelkonen and Grahne, 1975[8]	1/25	4
Atkinson et al, 1975[9]	0/10	0
Giovanelli et al, 1976[10]	0/29	0
Decker et al, 1976[11]	0/14	0
Hoi et al, 1977[12]	2/51	4
Milam et al, 1977[13]	0/16	0
Clemmons et al, 1979[14]	5/57	9
Law et al, 1979[15]	8/74	11
Tucker et al, 1980[16]	1/22	5
Baha et al, 1980[17]	2/28	7
Lindholm et al, 1981[18]	0/14	0
Richards and Thomas, 1980[19]	0/34	0
Schuster et al, 1981[20]	0/11	0
Teasdale et al, 1982[21]	0/56	0
Jadrevic et al, 1982[22]	2/64	3
	38/709	5.4

Second, the medical staff at our institution is familiar with the entity of "normal" growth hormone acromegaly and will, in spite of "normal" growth hormone levels, aggressively pursue the diagnosis of acromegaly in a patient with the appropriate clinical manifestations.

Third, all three cases were diagnosed since 1978 and, in fact, two of the three patients were diagnosed in 1982. Clearly, in recent years several new diagnostic procedures have become available that greatly aid in the diagnosis of pituitary tumors and acromegaly, in particular. A firm diagnosis of acromegaly was probably reached in some of our cases only because of the availability of CT scanning, somatomedin assays[14,23] and TRH stimulation tests.[24,25] Last, the number of cases of acromegaly seen at this medical center is small and therefore the high incidence of "normal" growth hormone acromegaly could be due to chance.

The mechanism by which acromegaly occurs despite "normal" growth hormone levels is unknown. Mims and Bethune have described in detail five cases of patients with acromegaly who have had normal basal growth hormone levels but whose growth hormone response failed to decrease during hyperglycemia or increase after levodopa administration, hypoglycemia, stress and sleep.[4] These authors postulated that fixed tumor production of high-normal levels of growth hormone could cause the signs and symptoms of acromegaly. Our three patients similarly showed abnormalities of growth response to various manipulations and, therefore, would support this hypothesis. It should be recognized that the presence of "normal" basal growth hormone levels does not rule out the possibility that these patients have intermittently elevated growth hormone levels. In fact, Cryer and Daughaday have reported several acromegalic patients with "normal" fasting growth hormone levels who, on continuous monitoring, had spikes of growth hormone secretion to very high levels.[26] It is possible that bursts of growth hormone release could have been undetected in our acromegalic pa-

tients and that these intermittent elevations in growth hormone concentration are enough to induce the abnormalities associated with acromegaly. Additionally, it is now recognized that human growth hormone is a complex of structurally different proteins with varying biologic activity.[27] It is possible that in our patients with "normal" growth hormone acromegaly the radioimmunoassay used failed to detect biologically active growth hormone.[28] However, it should be recognized that in most patients with acromegaly the radioimmunoassay of growth hormone has been shown to yield higher circulating levels than do biologic radioreceptor assays.[29] Occasionally, the clinical and radiologic findings of acromegaly in association with "normal" growth concentrations is due to "burnt out" acromegaly. This is not likely in our cases because our patients had the symptoms of acromegaly which resolved after surgical treatment and, on exploration of the pituitary, no evidence of infarction or hemorrhage into an adenoma was noted.

Last, readers should know that the absolute elevation in radioimmunoassayable growth hormone correlates poorly with the severity of the clinical syndromes of acromegaly.[14,30] Some investigators have reported that somatomedin levels, the putative mediator of the growth-promoting action of growth hormone, are a better reflection of disease activity.[14,23,31] In two of our patients in whom somatomedin levels were measured, they were elevated. Additionally, others have described cases of acromegaly with increased somatomedin levels and "normal" growth hormone concentrations.[14] It is possible that through a variety of mechanisms, elevations of somatomedin levels could occur in patients with "normal" growth hormone levels and thus result in the clinical manifestations of acromegaly.

Another interesting feature of our cases is that two of our three patients had acromegaly in the absence of an enlargement of the pituitary gland on radiographic examination. Similarly, two of the five patients with "normal" growth hormone acromegaly described in detail by Mims and Bethune also had normal-sized sellae.[4] The incidence of acromegaly in patients with a normal sella turcica on radiographic examination varies greatly from study to study, but, in general, the vast majority (more than 90%) of acromegalic patients have an enlarged sella turcica.[1,8,10,14,20,22] In two of our cases, a microadenoma was described both on CT scan and on pituitary exploration. It is tempting to postulate that the "normal" growth hormone levels and the presence of a microadenoma signify early disease, but both of our patients had the signs and symptoms of acromegaly for several years before diagnosis.

Based on our experience, it is important that clinicians recognize that acromegaly need not be associated with either elevations in basal growth hormone levels or radiographic enlargement of the pituitary gland. Clearly, if clinical findings suggest acromegaly, a "normal" basal growth hormone level or a normal sella turcica size on radiographic examination (or both) should not deter a physician from pursuing a diagnosis of acromegaly. There are several diagnostic tests that were helpful in confirming a diagnosis of acromegaly in our patients. These include a rise in serum growth hormone levels in response to TRH administration, failure of serum growth hormone concentrations to suppress below 5 ng per ml after glucose ingestion, and elevation in somatomedin levels and the presence of a pituitary microadenoma on a CT scan. Patients in whom the clinical diagnosis of acromegaly is suspected but not supported by basal growth hormone levels or routine x-ray films should have some or all of these diagnostic studies.

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